Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 10-22, 47 and 56-75 are pending in the application, with claims 10-12, 18, 20, 47 and 68-73 being the independent claims. Claims 10, 11, 12, 18, 20, 47, 68, 69, 70, 72 and 73 are sought to be amended. These changes are believed to introduce no new matter, and their entry is respectfully requested.

A request for continued examination (RCE) is being filed concurrently herewith. Therefore, the finality of the Office Action should be withdrawn, and the amendments presented herein should be entered and considered. 37 C.F.R. § 1.114(d).

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Support for Claim Amendments

Support for the amendment to claims 10, 11, 12, 18, 20, 47, 68, 69, 70, 72 and 73 can be found throughout the specification, for example, at page 10, lines 17-20, at page 70, lines 13-15, at page 71, lines 5-8.

II. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 10-22, 47 and 56-67 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention. (*See* Office Action dated

November 7, 2003, page 2.) According to the Examiner, "the new limitation of 'with the proviso that said one or more detectably labeled oligonucleotides do not comprise an acceptor molecule' in each of the independent claims appears to represent new matter." (*See id.*)

Applicants respectfully disagree with the Examiner's assessment. Nevertheless, solely to expedite prosecution, Applicants have deleted the expression "with the proviso that said one or more detectably labeled oligonucleotides do not comprise an acceptor molecule" from claims 10, 11, 12, 18, 20 and 47. In its place, Applicants have added the expression "wherein said detectable change in an observable property is not the result of a transfer of energy between two different compounds attached to said one or more oligonucleotides [or primers]."

Applicants believe that the newly added language accurately describes one of the new and unexpected aspects of the present invention, namely, that a detectable change in an observable property occurs when the detectably labeled oligonucleotide becomes part of a double stranded molecule, and that the detectable change in an observable property is not the result of a transfer of energy between two different compounds attached to the oligonucleotide (as in FRET-based methods). As noted in section I, above, the newly added language is fully supported by the specification.

In view of the amendment to claims 10, 11, 12, 18, 20 and 47, Applicants respectfully submit that the rejection under 35 U.S.C. § 112, first paragraph, has been fully accommodated and should be withdrawn.

III. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 10-22, 47 and 56-67 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. (*See* Office Action dated November 7, 2003, page 4.) This rejection is based on the term "acceptor." The Examiner stated that "there is no definition of this term in the specification and no mention of the term was even found in the specification. It is unclear what the scope of the term 'acceptor' is with regard to this claim." (*See id.*)

Applicants respectfully disagree with the Examiner's assessment. Nevertheless, Applicants note that none of the currently presented claims include the term "acceptor." Accordingly, the rejection under 35 U.S.C. § 112, second paragraph, is moot and should be withdrawn.

IV. Claim Rejections Under 35 U.S.C. § 102

A. Livak

Claims 10-17, 47, 56-58, 62, 64, 66, 67-70, 72 and 73 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Livak *et al.*, WO 96/15270 ("Livak"). (*See* Office Action dated November 7, 2003, page 5.) Applicants respectfully traverse this rejection.

An anticipation rejection under 35 USC § 102 requires a showing that each limitation of a claim is found in a single reference, practice, or device. *See In re Donohue*, 766 F.2d 531, 226 USPQ 619, 621 (Fed. Cir. 1985). As discussed below, Livak does not teach all of the elements of any of the currently presented claims.

1. Claims 10-17, 47, 56-58, 62, 64, 66 and 67

Claims 10-17, 47, 56-58, 62, 64, 66 and 67, as currently presented, are directed to methods involving the use of one or more oligonucleotides comprising one or more detectable labels. The detectable labels are located only internally. Moreover, the detectable labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule. The claims specify that the detectable change in an observable property is not the result of a transfer of energy between two different compounds attached to the oligonucleotides.

The method of Livak does not fall within the scope of claims 10-17, 47, 56-58, 62, 64, 66 or 67 First, the oligonucleotides used in the method of Livak all comprise a detectable label located at the 5' end. (*See* Livak at page 21, lines 17-19, and at page 22, Table 1.) That is, the oligonucleotides of Livak do not comprise one or more detectable labels located *only* internally.

The above-noted difference between Livak and the present claims (*i.e.*, that Livak does not teach oligonucleotides comprising one or more detectable labels located *only* internally) was noted in Applicants' previous response. (*See* Applicants' Reply Under 37 C.F.R. § 1.111, filed August 14, 2003, page 10.) In the final Office Action, the Examiner did not address this difference. The Examiner simply stated that:

> Applicant then argues the prior art rejections based upon their specific definition of the term "acceptor". Because the indefiniteness of this term is maintained and Applicant's definition is not accepted, the prior art rejections of Livak and Nazarenko are maintained.

(*See* Office Action dated November 7, 2003, page 15.) Since Applicants did not base their arguments regarding the novelty of the present claims over Livak (and Nazarenko) solely on

the meaning of the term "acceptor," it appears that the Examiner did not fully consider Applicants' arguments. Applicants respectfully request that the above-noted difference between Livak and the subject matter of the present claims be fully considered by the Examiner in assessing the novelty of the claims.

In addition to the fact that the oligonucleotides of Livak do not comprise one or more detectable labels located *only* internally, the method of Livak involves detecting changes in fluorescence that are caused by the transfer of energy between a reporter molecule and a quencher molecule that are attached to an oligonucleotide. (*See, e.g.*, Livak at page 7, lines 5-23.) By contrast, the present claims specify that the detectable change in an observable property is not the result of a transfer of energy between two different compounds attached to the oligonucleotides. Therefore, the method of Livak does not include all of the elements of claims 10-17, 47, 56-58, 62, 64, 66, 67-70, 72 or 73.

2. Claims 68-70, 72 and 73

Claims 68-70, 72 and 73 are directed to methods involving the use of one or more detectably labeled oligonucleotides that (a) comprise one or more detectable labels located *only* internally, and (b) are hairpin oligonucleotides.

The method of Livak does not fall within the scope of claims 68-70, 72 or 73. First, the oligonucleotides used in the method of Livak all comprise a detectable label located at the 5' end. (*See* Livak at page 21, lines 17-19, and at page 22, Table 1.) That is, the oligonucleotides of Livak do not comprise one or more detectable labels located *only* internally. (As noted in section IV.A.1, above, this difference was noted in Applicants' previous response but was not addressed by the Examiner in the final Office Action.)

Second, the oligonucleotides of Livak are not hairpin oligonucleotides. (*See* Livak at page 22, Table 1.) Therefore, the method of Livak does not include all of the elements of claims 68-70, 72 or 73.

3. Summary

Since the method of Livak does not include all of the elements of any of the currently pending claims, Livak cannot and does not anticipate claims 10-17, 47, 56-58, 62, 64, 66, 67-70, 72 and 73. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102, based on Livak, be reconsidered and withdrawn.

B. Nazarenko

Claims 18-22, 59-61, 66, 67 and 71 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Nazarenko *et al.*, *Nuc. Acids Res. 25*:2516-2521 (1997) ("Nazarenko"). (*See* Office Action dated November 7, 2003, page 6.) Applicants respectfully traverse this rejection. As discussed below, Nazarenko does not teach all of the elements of any of the currently presented claims.

1. Claims 18-22, 59-61, 66 and 67

Claims 18-22, 59-61, 66 and 67, as currently presented, are directed to methods involving the use of one or more oligonucleotides comprising one or more detectable labels. The detectable labels are located only internally. Moreover, the detectable labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule. The claims specify that the detectable change in an observable property is not the

result of a transfer of energy between two different compounds attached to the detectably labeled oligonucleotides.

The method of Nazarenko does not fall within the scope of claims 18-22, 59-61, 66 and 67. First, the oligonucleotides of Nazarenko all comprise a detectable label located at the 5' end. (*See* Nazarenko at page 2517, right column and Table 1, and at page 2518, left column.) That is, the oligonucleotides of Nazarenko do not comprise one or more detectable labels located *only* internally. (As noted in section IV.A.1, above, this difference was noted in Applicants' previous response but was not addressed by the Examiner in the final Office Action.)

Second, the method of Nazarenko involves detecting changes in fluorescence that are caused by the transfer of energy between two labels that are attached to an oligonucleotide. (*See, e.g.*, Nazarenko at page 2517, bottom left column.) By contrast, the present claims specify that the detectable change in an observable property is not the result of a transfer of energy between two different compounds attached to the oligonucleotides. Therefore, the method of Nazarenko does not include all of the elements of claims 18-22, 59-61, 66 or 67.

2. Claim 71

Claim 71 is directed to methods involving the use of one or more detectably labeled oligonucleotides that comprise one or more detectable labels located *only* internally. As discussed above, the oligonucleotides of Nazarenko do not comprise one or more detectable labels located *only* internally. (As noted in section IV.A.1, above, this difference was noted in Applicants' previous response but was not addressed by the Examiner in the final Office Action.) Therefore Nazarenko does not teach all of the elements of claim 71.

3. Summary

Since the method of Nazarenko does not include all of the elements of any of the currently pending claims, Nazarenko cannot and does not anticipate claims 18-22, 59-61, 66, 67 or 71. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102, based on Nazarenko, be reconsidered and withdrawn.

V. Claim Rejections Under 35 U.S.C. § 103

A. Heller in View of Nazarenko

Claims 68-75 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Heller, U.S. Patent No. 5,565,322 ("Heller") in view of Nazarenko. (*See* Office Action dated November 7, 2003, page 7.) Applicants respectfully traverse this rejection.

In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Since there is nothing in either Heller or Nazarenko to suggest combining or modifying the disclosures, a *prima facie* case of obviousness has not been established.

The rejection under § 103 is based on the Examiner's assertion that Heller indicates a need to improve the method described therein by reducing background fluorescence. As explained below, this is an incorrect assertion. Heller actually indicates that its system *solves* the problem of background fluorescence. There is nothing in Heller indicating that its method could or should be modified.

According to the Examiner, a person of ordinary skill in the art would have been

motivated to combine Heller and Nazarenko because "an ordinary practitioner using the Heller system is expressly motivated, in diagnostic applications, to reduce background using the Heller methodology and would be motivated to reduce background to as low a level as possible." (Office Action dated November 7, 2003, page 15.) To support this assertion, the Examiner cited the following passage from Heller:

> A multiple donor system comprised of such non-fluorescent chromophores would have very little inherent fluorescent background. This property overcomes a major limitation that has severely limited practical uses of fluorescent energy transfer in DNA diagnostic assay applications.

(Heller at column 10, lines 23-27.) This passage, however, does not suggest a need to modify the Heller method to reduce background fluorescence. To the contrary, this passage indicates that the Heller method itself has overcome the problem of inherent fluorescent background.

The "multiple donor system" to which Heller refers in the above-quoted passage is, in fact, the Heller system itself (*i.e.*, the "multiple donor system" is the system that is the subject of the Heller patent). Heller indicates that this multiple donor system "would have very little inherent fluorescent background." Thus, Heller does not suggest a need to improve or modify this system.

The fact that Heller does not indicate a need to improve or modify its system is made even more clear when one considers the paragraph immediately preceding the passage cited by the Examiner:

> A non-fluorescent donor producing fluorescent re-emission in the acceptor group is an extremely valuable property. The non-fluorescing donor in a composition of *the present invention provides the particular advantage of a low*

> *or absent level of emission by the donor*, thereby not contributing to background or the detectable emitted light in a donor-acceptor system. Thus, non-fluorescent donors allow for very low background and are particularly preferred.

(Heller at column 10, lines 15-22, emphasis added.)

Since Heller indicates that the method set forth therein solves the problem of background fluorescence, a person of ordinary skill in the art would have had no motivation to modify the Heller method to "reduce background."

Moreover, the system described in Heller is designed to transfer photonic energy over long distances by relaying the energy between multiple donors to an acceptor.

> It has now been discovered that multiple chromophore donor groups which are located beyond the normal Förster distance (>5 nm) can be arranged to absorb and transfer photonic energy to a terminal acceptor group thereby acting as a light antenna or photonic conductor.

(Heller at column 4, lines 28-32; *see also* Figs. 1B and 3B.) Therefore, introducing a hairpin structure into the Heller oligonucleotides would appear to defeat the ultimate purpose of the invention. Hairpin conformations *reduce* the distance between donors and acceptors attached to the hairpin. Thus, if the oligonucleotides of the Heller system were in a hairpin conformation, the signal would no longer be relayed between multiple donors to an acceptor over a long distance.

In sum, Heller indicates that its system overcomes the problem of background fluorescence. In addition, the purpose of the Heller system would be defeated by including hairpin structures into the oligonucleotides set forth therein. Therefore, a person of ordinary skill in the art would not be motivated to modify the disclosure of Heller or combine it with that of Nazarenko. (Applicants note that these arguments were presented in their previous

response but were not addressed by the Examiner in the final Office Action.) Applicants respectfully request that the rejection of claims 68-75 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

B. Nazarenko

Claims 18-22, 59-61, 63-67 and 71 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nazarenko. (*See* Office Action dated November 7, 2003, page 10.) Applicants respectfully traverse this rejection.

In order to establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Since Nazarenko does not teach or suggest all of the elements of the claims, a *prima facie* case of obviousness cannot be established.

As discussed above, the claims as currently presented, are directed to methods involving the use of one or more oligonucleotides comprising one or more detectable labels. The detectable labels are located only internally. Moreover, as specified in claims 18-22, 59-61 and 63-67, the detectable labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule, and the detectable change in an observable property is not the result of a transfer of energy between two different compounds attached to the oligonucleotides.

The oligonucleotides of Nazarenko comprise a detectable label on the 5' end (*i.e.*, do not comprise one or more detectable labels located *only* internally). (As noted in section IV.A.1, above, this difference was noted in Applicants' previous response but was not addressed by the Examiner in the final Office Action.) In addition, the method of Nazarenko

involves detecting changes in fluorescence that are caused by the transfer of energy between two labels that are attached to an oligonucleotide. Therefore, Nazarenko does not teach or suggest all of the elements of the present claims. Accordingly, a *prima facie* case of obviousness cannot be established. Applicants respectfully request that the rejection of claims 18-22, 59-61, 63-67 and 71 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Frank R. Cottingham

Frank R. Cottingham
Attorney for Applicants
Registration No. 50,437

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1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600